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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/751,056	01/02/2004	**Gerianne Tringali DiPiano**	FEM 104	1945

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EXAMINER	
KIM, JENNIFER M	
ART UNIT	**PAPER NUMBER**
1617	

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03/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/751,056	**Applicant(s)** DIPIANO ET AL.	
	Examiner Jennifer Kim	**Art Unit** 1617	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 March 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-8*.
   Claim(s) withdrawn from consideration: *10-15 and 17-19*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☒ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). 3/7/2008
13. ☐ Other: _____.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Continuation of 11. does NOT place the application in condition for allowance because: The claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references.
With regard to 35 U.S.C. 112, first paragraph rejection, Applicants argue that the examiner has provided no basis for the rejection other than an allegation that the claims are broad. This is not found persuasive because the rejection formulated with consideration based on all the Wands factors. (see Final rejection). While the state of the art is relatively high with a formulation comprising a specific drug and a specific penetration enhancer (e.g. 4-hydroxytamoxifen and triethanolamine), the state of the art with regard to a formulation comprising a drug with a penetration enhancer is underdeveloped. The cited Reed reference teaches that there is problem with most known dermal penetration enhancers that they are often toxic, irritating allergenic. Reed further teaches that these difficulties remain with those dermal enhancers because the problem of irritation at the site of application has not been overcome. Reed further teaches some of enhancers are that are toxic and unsuitable for application for the animal body. Moreover, Reed teaches that the thermodynamic activity of a drug with vehicles can cause precipitation causing ceases percutaneous absorption. To the extent that instant claims drawn to a drug formulation comprising any drug with any penetration enhancer to promote delivery of the drug across the stratum corneum, which is highly speculative, a great amount of evidence is required to show its operability on actual loci in human. Applicants' argue that it is well within the abilities of one of skill in the art to select a drug and a penetration enhancer as exemplified for danazol and 5% oleyl alcohol, in order to make the claimed formulation. This is not persuasive because Applicants' example comprising a single drug (i.e. danazol) with a penetration enhancer does not enable all drugs with all penetration enhancer. Given the fact that the most known dermal penetration enhancers are taught to be problematic as being toxic, irritating allergenic, and the difficulties remain with those dermal enhancers because of the problem of irritation at the site of application has not been overcome, the scope enablement made in the previous Office Action is deemed proper.
With regard to 35 U.S.C. 102 rejection, Applicants argue that Jarvis disclosed the treatment of breast cancer comprising administering an anti-estrogen drug which is derived from tamoxifen. However, the claims have been amended to clearly exclude delivery of drugs for treatment of breast cancer, by incorporating the limitation of claim 9 and 16 into claims 1 and 10, wherein the disease is benign (not cancer, not malignant). This is not found persuasive because Applicants attention is drawn to the abstract, wherein Mauvais-Jarvis et al. (Jarvis) teaches that the anti-estrogen drug (4-hydroxytamoxifen) is applicable in the treatment of conditions of the breast, especially benign (not cancer; not malignant) and even cancerous conditions of the breast. (column 4, lines 37-40). Therefore, this reference clearly anticipates the currently amended treatment of "benign" (not cancer; not malignant) conditions of the breast. Applicants argue that Applicants are unclear as to the Examiner's reason for concluding that triethanolamine is employed as a penetration enhancer in Jarvis, considering the numerous other applications for the compound because there is nothing in Jarvis that supports such a conclusion. This is not found persuasive because Jarvis teaches that the drug can be administered percutaneously preferably topically to a breast. (column 2, lines 29-32, column 3, lines 13-15, lines 52-57). One of ordinary skill in the art would immediately envision that triethanolamine employed by Jarvis is a penetration enhancer because Jarvis teaches the topical administration via percutaneously absorption to a breast as a preferred route. Further, triethanolamine is a well known penetration enhancer as evidenced by Oden reference. Therefore, the rejection stands.
With regard to 103 rejection, Applicants argue that the examiner's conclusion of obviousness is based upon improper hindsight reasoning. This is not persuasive because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Applicants argue that Ragaven1 (U.S.Patent No. 5,993,856) is silent about including penetration enhancers in the formulation. This is not found persuasive because Ragavan 1 clearly teaches the utilization of triethanolamine or sorbitan esters with danazol. (column 3, lines 25-37). As indicated above, the triethanolamine is a well known penetration enhancer as evidenced by Oden reference. Applicants argue that "Region" is defined in Ragavan 1 as reproductive organs and their surrounding environs, which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and the rectovaginal region, therefore, formulation disclosed in Ragavan 1 are meant for delivery across mucosal membranes. This is not found persuasive because Applicants are reminded that the instant claims are drawn to a "drug formulation". Applicants' recitation of the intended use of promoting delivery of the drug across the stratum corneum must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended delivery, then it meets the claim. In this case, Ragavan 1 teaches the same active agent (danazol), the same penetration enhancer (e.g. triethanolamine) and the same "amount effective to provide relief from benign dieses or disorder". Therefore, Ragavan1's formulation would have the same functional characteristics such as promoting delivery of the drug across the stratum corneum. Applicants argue that Alginic acid is widely used a disintegrant promoting rapid breakdown of tablets to rapidly release the active agent but the same agent at higher concentration is employed to delay release of active agent form formulation which is the exact opposite effect obtained with a disintegrant. This is not found persuasive because alginic acid and its properties are not at issue. The issue is that compound, triethanolamine utilized in Ragavan 1 is "a penetration enhancer" as required by instant claims.
With regard to Double Patenting Rejection, Applicants argue that the instant claims differ with Claims of Ragavan 1, Ragavan 2 and Ragavan 3: in drug to be delivered; in region to be treated; need for excipient; for treatment of different disorders. This is not found persuasive because the drug to be delivered is obvious variation of one another because reproductive disorder includes breast disorder as breast is well known reproductive organ); the region to be treated is obvious variation because the patented claims drawn to the regions of reproductive organ would obviously encompasses breast region; need or excipient is obvious variation because a penetration enhancer itself is an excipient. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.